REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the remarks that follow. Claims 16-30 are pending in the application.

Claims 16-30 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of U.S. Patent No. 5,484,601 to O'Leary *et al.*, U.S. Patent No. 5,385,887 to Yim *et al.*, and the WO 98/40113 reference listing Wironen as an inventor. Applicants respectfully traverse this rejection.

Applicants again reiterate that one of ordinary skill in the art would have no motivation to combine the three references of the rejection in the manner contemplated by the Examiner. Specifically, the art provides no motivation for combining the Yim and Wironen references with the O'Leary reference in the manner relied upon by the Examiner.

The Examiner relies on language in the Yim reference regarding reduction in set-up time and improvement in handling, moldability and consistency as evidence of a motivation to combine the calcium sulfate hemihydrate of Yim with the formulation of O'Leary. However, Yim does not provide a general suggestion that calcium sulfate provides such advantages in any bone graft composition. Instead, the Yim reference only suggests that a calcium sulfate hemihydrate-containing substance (CSHS) provides such advantages when combined with the formulation described in U.S. Pat. No. 5,171,579 (see column 2, lines 51-65). Yim only suggests a CSHS provides such advantages in the context of a formulation comprising osteogenic proteins, autogenous blood, and a porous particulate polymer matrix, such as a copolymer of lactic acid and glycolic acid (PLGA). There is no suggestion in the Yim reference that such improved properties would be expected in any other formulation. Yim merely teaches that, "[t]o reduce the preparation time and improve the above formulation's handling characteristics" (emphasis added), a CSHS can be added. The "above formulation" is the formulation described in the '579 patent, which includes an osteogenic protein, autogenous blood, and a porous particulate polymer matrix. Since the composition in the O'Leary reference is not a combination of osteogenic proteins with autogenous blood and a porous particulate polymer matrix such as

PLGA, there would be no motivation to combine the CSHS of Yim with the composition described in O'Leary for the reasons suggested by the Examiner.

The Examiner dismisses this argument by stating that the "above formulation" in column 2 of Yim refers to formulations including a protein-sequestering agent and points to the list of optional protein-sequestering agents in column 7. The fact that Yim mentions other optional protein-sequestering agents later in the disclosure does nothing to change the clear context of the reference's teachings in the first paragraph of the detailed description section. Yim first describes a composition found in the '579 patent and then, in the same paragraph, refers to the "above formulation" when discussing the beneficial handling characteristics that can be achieved by adding calcium sulfate hemihydrate. The clear implication of this paragraph is to suggest that the composition of the '579 patent, which includes a porous particulate polymer matrix and autogenous blood, can be improved by adding calcium sulfate hemihydrate. One of ordinary skill in the art would not view this teaching as relevant to O'Leary, which does not describe a formulation including autogenous blood or a porous particulate polymer matrix. The Examiner notes that Yim "already includes the thickener of O'Leary yet finds that the addition of calcium sulfate improves the composition for certain applications" (page 4, Office Action dated 6/15/04) (emphasis in original). While it is true that Yim teaches a list of optional protein-sequestering agents that includes cellulosic materials, such a teaching has no bearing on the central question of whether Yim would have motivated one of ordinary skill in the art to add calcium sulfate hemihydrate to the formulation of O'Leary. The key point is that Yim teaches the advantages of calcium sulfate only in certain applications. With respect to the beneficial effects of calcium sulfate mentioned by Yim *et al.* in column 2 and relied upon by the Examiner, the "certain application" is the formulation disclosed in the '579 patent, which clearly contains key ingredients not found in the O'Leary formulation. Thus, the fact that the Yim reference suggests a method of improving the handling characteristics of the formulation of the '579 patent does not translate into motivation to add calcium sulfate hemihydrate to the markedly different formulation of O'Leary.

In addition, as noted previously, there is nothing in the O'Leary reference to suggest a problem with moldability, consistency, etc. of the formulation described therein that might lead

one of ordinary skill in the art to seek an additive to address such a problem. Indeed, the O'Leary patent suggests that the consistency of the "flowable" material can be adjusted simply by altering the amount of the organic liquid component (column 3, lines 28-35). The Examiner responds that "Applicants do not take into consideration that O'Leary envisions a range of consistencies." Actually, Applicants are fully aware of the wide range of consistencies contemplated by O'Leary, which is the whole point of the section of O'Leary referenced above. The portion of O'Leary cited by Applicant above states that "the liquid component of the composition serves to provide a flowable material of widely varying consistency" (column 3, lines 30-32) (emphasis added). The "liquid component" referred to in this quote is the organic carrier material of the O'Leary formulation. Thus, O'Leary teaches that a flowable material of widely varying consistency can be achieved using the organic liquid component. This is clear evidence that one of ordinary skill in the art would not view an additional ingredient as necessary to improve moldability, consistency, etc. of the O'Leary formulation. Instead, O'Leary suggests that the organic liquid carrier itself can be used to manipulate such characteristics.

As admitted by the Examiner, the Yim reference only teaches that calcium sulfate improves a composition in certain applications. As explained above, there is no basis for concluding that one of ordinary skill in the art would have been motivated to combine the teachings of Yim with the teachings of O'Leary as contemplated by the Examiner, and Applicants respectfully request reconsideration and withdrawal of the rejection of record for this reason.

In addition, Applicants continue to submit that there is no motivation to combine the teachings of the Wironen reference with the teachings of either O'Leary or Yim. The composition described in the Wironen reference is so fundamentally distinct from the compositions described in the Yim and O'Leary references that one of ordinary skill in the art would clearly view such differences as weighing against the combination suggested by the Examiner. The Wironen reference describes a bone paste that contains thermally crosslinkable gelatin as the carrier for one or more osteogenic components. The gelatin-based composition has the unique ability to exhibit thermoreversible gelation properties that allow the composition to be a fluid at a temperature above normal body temperature and a solid gel at body temperature (see

page 7, line 27- page 8, line 6; page 11, lines 21-26; page 12, lines 9-14). Neither the O'Leary nor Yim references are directed to gelatin-based compositions exhibiting thermoreversible gelation characteristics. The Examiner opines that Applicant's analysis is "piecemeal" and fails to address the teachings of the reference as a whole. However, Applicants could say the same for the Examiner's description of this reference, since the Office Action includes a list of numerous possible ingredients of the Wironen composition without mentioning gelatin, which comprise 20-45% of the composition and acts as a carrier for the remaining components. Gelatin is a crucial ingredient in the Wironen composition and yet the Office contends that one of ordinary skill in the art would be motivated to pluck, in piecemeal fashion, the cancellous bone from the Wironen disclosure and combine it with the O'Leary composition. Applicants respectfully submit that a fair reading of Wironen would only suggest to one of ordinary skill in the art that cancellous bone chips could be useful as an additive in a gelatin-based composition that exhibits thermoreversible gelation properties. It is particularly inappropriate to suggest a combination of an optional ingredient of Wironen with the O'Leary composition where, as noted in the previous response, Wironen actually teaches away from the O'Leary composition on page 3. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection and formal notification of the allowability of all claims as now presented.

Additionally, Applicants again submit that even if the three references are properly combinable, the resulting combination would surely fail to suggest any of the formulations recited in Claims 23-30, which recite a specific combination of ingredients including a specific amount of cancellous bone. There is no suggestion in the Wironen/Yim/O'Leary references to form the particular combinations of ingredients and relative amounts set forth in Claims 23-30. The Wironen reference fails to suggest <u>any</u> concentration for the optional cancellous bone ingredient. No guidance is provided whatsoever as to the amount of cancellous bone chips, yet the Examiner alleges that each of the combinations recited in Claims 23-30 would be obvious. The Examiner responds that "optimization of amounts is equally within the skill of the practitioner." However, an argument based on "optimization" of an amount or range assumes the prior art teaches <u>some</u> amount or range, which is clearly not the case here. Wironen provides absolutely no guidance on the amount of cancellous bone, so there is nothing in the cited art to

optimize. To establish *prima facie* obviousness of a claimed invention, all the claimed limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). It has been noted repeatedly by the courts that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494,496 (CCPA 1970). The Examiner notes that Applicants have not provided any evidence of surprising results, but such a showing is not required when, as in this case, the Office has not met its burden of establishing unpatentability in the first instance. For this additional reason, Applicants respectfully submit that Claims 23-30 are patentable over the cited references.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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